Comparison of *in vitro–in vivo* release of Risperdal® Consta® microspheres

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ABSTRACT

The objective was to investigate the relationship between *in vitro* and *in vivo* release of commercial Risperdal® Consta® microspheres. A modified USP apparatus 4 method was used for accelerated and real-time *in vitro* release testing. The *in vivo* plasma profile (clinical data) reported for the product was deconvoluted for comparison with the *in vitro* release profiles. The *in vivo* profile differed from the real-time *in vitro* profile and was faster initially and then slower after approximately 30 days. This effect is considered to be due to differences in the *in vivo* conditions such as small interstitial volume, low pH and immune response. Accelerated *in vitro* release profiles obtained at temperatures (50 °C and 54.5 °C) above the microsphere glass transition temperature (Tg ∼ 48 °C) overlapped with the *in vivo* profile after time scaling. A linear *in vitro–in vivo* relationship was observed with correlation coefficients of 0.97 and 0.99 at 50 °C and 54.5 °C, respectively. The accelerated test performed below the Tg had a similar release profile to that of the real-time *in vitro* test. The accelerated tests performed above the Tg of the microspheres showed the potential to be used for *in vivo* performance prediction as well as for quality control purposes.

1. Introduction

In the past few decades, significant medical advances have been made in the area of drug delivery with the development of novel dosage forms. Controlled release parenteral formulations (*e.g.* microspheres, liposomes, implants and drug eluting stents) are gaining popularity due to the advantages of lower dosing frequency and hence better patient compliance; reduced adverse affects as a result of small amounts of targeted and localized drug delivery; and improved therapeutic response due to consistent drug blood levels. Controlled release parenteral poly(lactide-co-glycolide) (PLGA) microspheres are often used to achieve drug release extended over days to months. The drug release from PLGA microspheres is controlled by drug diffusion, polymer erosion or a combination of both. Accordingly, different phases of drug release (representing different mechanisms of release) are observed in the release profile of PLGA microspheres (Faisant et al., 2002; Zolnik et al., 2006).

The development and regulatory approval of special dosage forms such as controlled release parenteral microspheres is hindered by the lack of standard *in vitro* release test methods. *In vitro* release is an important test that facilitates formulation development and is used to assess quality and *in vivo* product performance. An *in vitro* release test with *in vivo* relevance is preferred as it saves time and cost of performing bio-studies (*In vitro–in vivo correlation* can be used to obtain bio-waiver). However, a one-to-one correlation between *in vitro* and *in vivo* profiles is often not observed for PLGA microspheres due to the difference in conditions (*in vitro* and *in vivo*) which results in different release mechanisms (Zolnik and Burgess, 2008). The factors that may contribute to the change in the release mechanism under *in vivo* conditions include: (1) small interstitial fluid volume at subcutaneous and intramuscular sites; (2) accumulation of acidic degradation products in the vicinity of the microspheres resulting in PLGA autocatalysis; (3) enzyme catalyzed polymer degradation; (4) inflammatory reaction to the injected microspheres; and (5) biological barriers to drug diffusion and absorption (*e.g.* fluid viscosity, drug permeation through capillary endothelium or lymphatics) (Holland and Tighe, 1986; Makino et al., 1985; Williams and Mort, 1977; Zolnik and Burgess, 2008). There are only a few examples in the literature where *in vitro–in vivo* correlation/relationship has been reported for controlled release parenteral microspheres (Schliecker et al., 2004; Vlugt-Wensink et al., 2007; Zolnik and Burgess, 2008). The complex nature of these drug delivery systems and multi-phase release characteristics sometimes necessitates establishing correlation for different phases separately (Young, 2007; Zolnik and Burgess, 2008).

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The US FDA (Food and Drug Administration) has categorized *in vitro–in vivo* correlation (IVIVC) into five main levels: level A, B, C, multiple level C and D. Level A represents point-to-point correlation between *in vitro* and *in vivo* profiles. A Level B correlation utilizes statistical moment analysis comparing a mean *in vitro* dissolution time to either a mean *in vivo* residence or dissolution time. Level C IVIVC establishes a single point relationship between a dissolution parameter such as time required for 50% dissolution and a pharmacokinetic parameter such as C_{max} or AUC. A multiple level C IVIVC relates multiple dissolution time points to one or more pharmacokinetic parameters (*e.g.* C_{max} or AUC). Level D is a rank order correlation (FDA Guidance for Industry, 1997). IVIVC is usually established using two or more formulations with different rates of release and a level A IVIVC is needed for the *in vitro* release method to be used as a surrogate for bioequivalence studies. *In vitro–in vivo* relationship (IVIVR) is a more general term which allows linear as well as non linear relationships between *in vitro* release and *in vivo* absorption (using single or multiple formulations) (Emami, 2006; Young, 2007).

Accelerated *in vitro* release methods (using elevated temperature, extreme pH or co-solvents) are required for development and quality control of controlled release formulations due to their long term release duration (weeks to months). The design of an *in vitro* release test method depends on the test objective. While a simple accelerated *in vitro* method may be preferred for quality control purposes, more complex conditions are needed to establish a bio-relevant method. Therefore, separate *in vitro* release methods may be developed for quality control and *in vivo* performance prediction (Martinez et al., 2008). However, it would be ideal to have one method that serves both the purposes as the ultimate goal of a quality control test is to ensure clinical performance (*i.e.* safety and efficacy) of the product (Burgess et al., 2004).

In the present study, a commercial Risperdal® Consta® 25 mg long acting injection (risperidone microspheres) was used to investigate the relationship between *in vivo* and *in vitro* release. The *in vivo* plasma profile (clinical data) reported for the product was deconvoluted for comparison with the *in vitro* release profiles (Eerdekens et al., 2004). A USP apparatus 4 method was used for real-time and accelerated *in vitro* release testing of the microspheres as it has been shown to be able to discriminate between different microsphere formulations and has been recommended for controlled release parenterals (Burgess et al., 2004; Rawat and Burgess, 2010; Zolnik and Burgess, 2008; Zolnik et al., 2006).

2. Materials and methods

2.1. Materials

Acetonitrile (HPLC grade) were purchased from Fisher Scientific (Pittsburg, PA). Risperidone and trifuoroacetic acid were purchased from Sigma–Aldrich (St. Louis, MO). Nanopure™ quality water (Barnstead, Dubuque, IA) was used for all studies. Risperdal® Consta® 25 mg long acting injection (risperidone microspheres) (batch numbers: 176921, 168800, 169941, 9BA231, 9BA237, 8MA071, 9MA575 and 8JA816; Ortho McNeil-Janssen) were purchased from University of Connecticut, Student Health Services pharmacy.

2.2. Methods

2.2.1. Characterization of drug and microspheres
2.2.1.1. *High performance liquid chromatography (HPLC).* The concentration of risperidone was determined using a Perkin Elmer HPLC system (series 200) with a UV absorbance detector (Perkin Elmer) set at 275 nm. The mobile phase was acetonitrile:water:trifluoroacetic acid (25:75:0.1%, v/v/v). An Agilent C18 stable bond (4.6 mm × 15 cm) column was used with the flow rate set at 1 ml/min. The chromatographs were analyzed using PeakSimple™ Chromatography System (SRI instruments, Torrace, CA). An injection volume of 30 μl was used for drug release samples. This method is a stability indicating HPLC assay.

2.2.1.2. *Risperidone stability.* Risperidone stability in 0.05 M phosphate buffer saline pH (PBS) 7.4 was determined at different temperatures. Risperidone solutions (5 μg/ml) in PBS were incubated in water baths maintained at 37 °C, 45 °C, 50 °C, 55 °C and 60 °C. Degradation of risperidone was monitored using HPLC for 30 days at 37 °C and for 6 days at 45, 50, 55 and 60 °C. All measurements were conducted in triplicate.

2.2.1.3. *Glass transition temperature.* The glass transition temperature of the microspheres was analyzed using a TA instrument Q100 differential scanning calorimeter (DSC). Samples were heated from −40 °C to 100 °C, cooled to −40 °C and heated again to 100 °C at a rate of 20 °C/min. The first cycle of the thermograms was used to determine the glass transition temperature (Tg) of the microspheres. All measurements were conducted in triplicate and the results are reported as the mean ± SD.

2.2.1.4. *In vitro release.* A modified USP apparatus 4 (Sotax CE7 smart with CY 7 piston pump, Sotax, Horsham, PA) was used for *in vitro* release testing (Zolnik et al., 2005). Flow through cells (12 mm diameter) packed with 9 gm of glass beads (1 mm diameter) were used in a closed system. The flow through cells were prepared by filling 1/3rd of the cells with 1 mm diameter glass beads. About 10 mg of microspheres were weighed and divided into three approximately equal parts. The first part was placed over the glass beads in the cells and one small scoop of glass beads was added thereafter. This process was repeated for the second and third parts of the microspheres. The cells were filled with the remaining glass beads up to the brim. An anti-static gun was used to neutralize static charge on the glass beads, microspheres and spatula to facilitate sample preparation. 250 ml of 0.05 M phosphate buffer saline (PBS) pH 7.4 with 0.1% sodium azide was circulated through the flow through cells (fitted with regenerated cellulose filter 0.45 μm) at a flow rate of 8 ml/min. The temperature of the Sotax USP apparatus 4 was maintained at 37 ± 0.1 °C for the real-time studies. The accelerated *in vitro* release testing was performed at 45 ± 0.1, 50 ± 0.1 and 54.5 ± 0.1 °C. The release medium was de-aerated using the USP method (USP General Chapter ⟨711⟩) before starting the release test. De-aeration during the test was performed using helium sparging in the media bottles. One milliliter samples were withdrawn and replaced with fresh media at suitable time intervals. The samples were analyzed using HPLC as described before using an injection volume of 30 μl. Release medium was replaced with fresh media at appropriate time intervals to maintain sink conditions. The medium replacement during the release study was taken into account in the calculation of fraction released. All measurements were conducted in triplicate and the results are reported as the mean ± SD.

2.2.1.5. *Plasma profile deconvolution.* The plasma profile of Risperdal® Consta® 25 mg long acting injection (risperidone microspheres), reported in the literature, was used for determining the relationship with the *in vitro* release profile (Eerdekens et al., 2004). The plasma profile was deconvoluted using the Loo-Riegelman method (Shargel et al., 2005). Deconvolution was performed using the average plasma concentration values. Therefore, the standard error cannot been shown in the deconvoluted
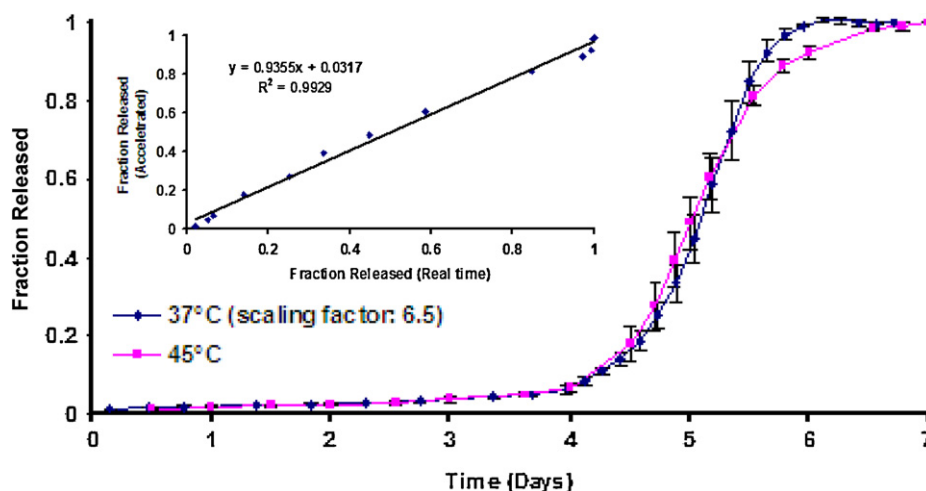
Fig. 1. *In vitro* release profiles of Risperdal® Consta® 25 mg long acting injection (risperidone microspheres) in 0.05 M PBS pH 7.4 at 37 °C (time scaled) and 45 °C (*n* = 3). Insert shows linear correlation between real time (37 °C) and accelerated (45 °C) fraction released.

absorption profile. The fraction absorbed *in vivo* was calculated as:

$$\frac{Ab}{Ab_\infty} = \frac{C_p + C_t + k_{10}(AUC)_0^t}{k_{10}(AUC)_0^\infty}$$

C_p, C_t, k_{10} and (AUC) are the drug concentration in central compartment (plasma), apparent tissue compartment concentration, elimination rate constant and area under the plasma *vs.* time curve, respectively. The distributive and elimination micro rate constants (k_{12}, k_{21} and k_{10}), needed for calculating C_t, were determined using GastroPlus™ software (Simulations Plus, Inc., CA) from the reported risperidone intravenous data (Huang et al., 1993).

3. Results

3.1. Risperidone stability at elevated temperature

Risperidone stability determined in 0.05 M PBS pH 7.4 at 37 °C (for 30 days) and at 45, 50, 55 and 60 °C (for 6 days) showed no change at 37, 45, 50 and 55 °C. However, a degradation peak was observed in the HPLC chromatogram at 60 °C after day 2.

3.2. Glass transition temperature

The glass transition temperature of the microspheres was determined as 48.84 ± 0.34 °C.

3.3. In vitro release

A biphasic *in vitro* release profile (*i.e.* a lag phase of 24 days followed by the release phase up to day 40), after an initial fraction burst release of 0.016, has been previously observed for Risperdal® Consta® 25 mg long acting injection (risperidone microspheres) at 37 °C (Rawat and Burgess, 2011). The release duration reduced from approximately 40 days (at 37 °C) to 7 days under accelerated conditions (45 °C) and a good correlation (R^2 = 0.9929) was observed between the two profiles after time scaling as shown in Fig. 1. Higher temperatures *i.e.* 50 and 54.5 °C were investigated in the present work for accelerated release testing of the microspheres. As shown in Fig. 2, the release duration was further reduced to approximately 3 and 2 days at 50 and 54.5 °C, respectively. However, unlike at 45 °C the release profiles at 50 and 54.5 °C did not overlap with the real-time profile (time scaled) (Figs. 3 and 4). The lag phase was not as prominent as in the *in vitro* release profiles
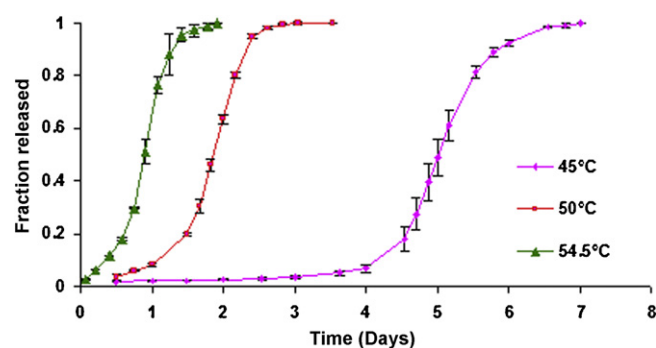

Fig. 2. *In vitro* release profile of Risperdal® Consta® 25 mg long acting injection (risperidone microspheres) in 0.05 M PBS pH 7.4 at 45, 50 and 54.5 °C (*n* = 3).

at 45 and 37 °C. The correlation coefficient (R^2) between accelerated (50 and 54.5 °C) and real-time profiles were approximately 0.95 (Figs. 4 and 6). Scaling factors were determined as the ratio of time to 50% drug release under real time and accelerated release conditions.

3.4. Plasma profile deconvolution

The plasma concentration *vs.* time profile of intravenous risperidone showed a bi-phasic decay and hence can be described by the
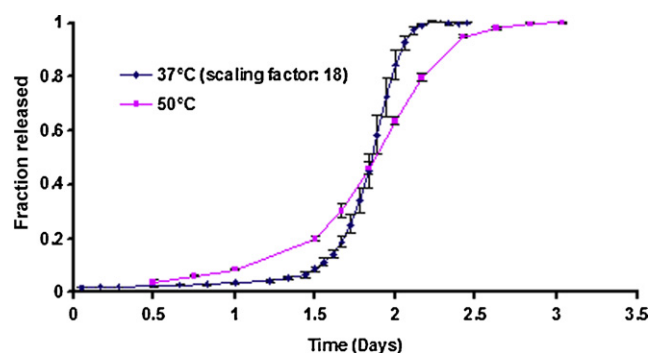

Fig. 3. *In vitro* release profiles of Risperdal® Consta® 25 mg long acting injection (risperidone microspheres) in 0.05 M PBS pH 7.4 at 37 °C (time scaled) and 50 °C (*n* = 3).
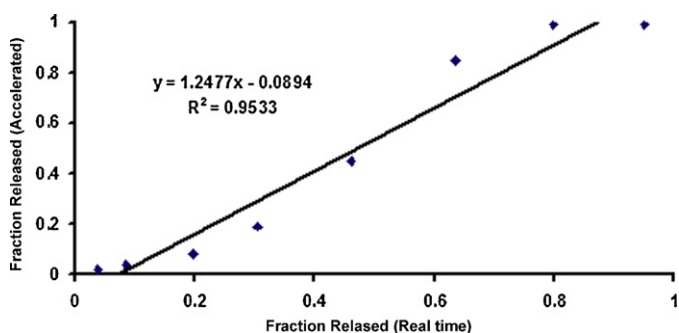
Fig. 4. Correlation between real time (37 °C) and accelerated (50 °C) fraction released.
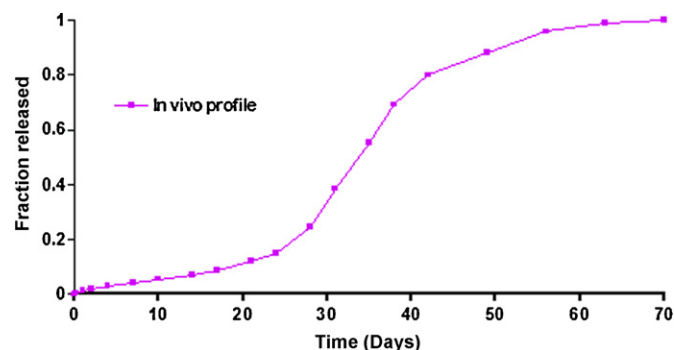

Fig. 5. *In vitro* release profiles of Risperdal® Consta® 25 mg long acting injection (risperidone microspheres) in 0.05 M PBS pH 7.4 at 37 °C (time scaled) and 54.5 °C (*n* = 3).

two compartment model according to the equation (Huang et al., 1993; Peer and Meuldermans, 1996):

$$C_p = Ae^{-\alpha t} + Be^{-\beta t}$$

where C_p is the plasma concentration of risperidone at time t; A and B are empirical constants; α and β are the hybrid rate constants of the distribution and elimination phases, respectively. The constants A, B, α and β are determined from the intercepts and slopes of the intravenous plasma *vs.* time curve and micro rate constants are calculated from determined distribution and elimination constants (*i.e. A*, B, α and β).

GastroPlus™ software (Simulations Plus, Inc., CA) was used for determining the pharmacokinetic parameters of risperidone from the reported intravenous plasma concentration *vs.* time profile (Huang et al., 1993). As shown in Table 1, the micro rate constants k_{12}, k_{21} and k_{10} were determined as 0.156, 0.131 and 0.105 h^{-1}, respectively. The half-life calculated for risperidone is 19 h using GastroPlus™ software (Simulations Plus, Inc., CA) from

Fig. 6. Correlation between real time (37 °C) and accelerated (54.5 °C) fraction released.

Fig. 7. *In vivo* profile (plasma profile*) of Risperdal® Consta® 25 mg long acting injection (risperidone microspheres) deconvoluted using the Loo-Riegelman method. *Plasma concentration *vs.* time profile from reference (Eerdekens et al., 2004).

the terminal elimination phase ($t_{1/2} = 0.693/\beta$). This is in good agreement with reported value of approximately 20 h for the active moiety (risperidone and its active metabolite 9-hydroxyl risperidone) (Huang et al., 1993).

The Loo-Riegelman method was used for plasma profile deconvolution since the pharmacokinetics of risperidone has been reported to follow a two compartmental model (Huang et al., 1993). The plasma profile of Risperdal® Consta® 25 mg long acting injection (risperidone microspheres) deconvoluted using the Loo-Riegelman method (refer Section 2.2.1.5) is shown in Fig. 8 (Eerdekens et al., 2004; Shargel et al., 2005). The deconvoluted *in vivo* profile showed a lag phase of approximately 24 days after an initial fraction absorbed (due to burst release) of approximately 0.02. Approximately 15% of the drug was absorbed during the 24 days lag phase. The fraction of drug absorbed increased gradually after day 24 and a plateau was reached by day 56 (Fig. 7).
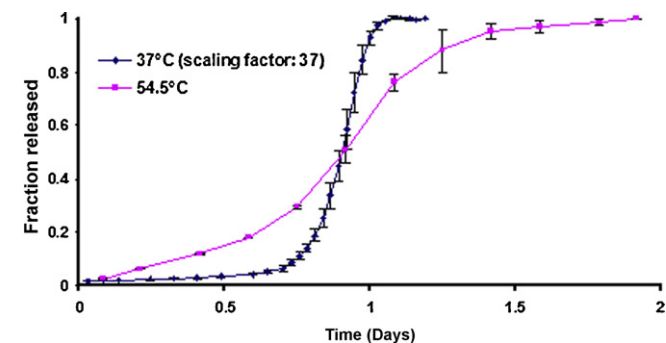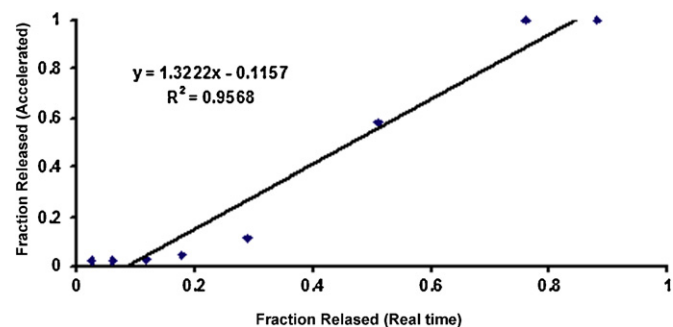
3.5. Comparison of in vitro and in vivo profiles

A comparison of real-time *in vitro* release (37 °C) and *in vivo* absorption profiles showed a lag phase of similar duration (~24 days) followed by a steady increase in drug released/absorbed after day 24. However, the fraction absorbed *in vivo* was higher than the fraction released *in vitro* (real-time) during the lag phase as shown in Fig. 8. The real-time *in vitro* release of risperidone from the microspheres was complete in approximately 40 days whereas the plateau was reached in approximately 56 days in the *in vivo* absorption profile. The *in vivo* profile was faster than the *in vitro* profile in the beginning (up to 30 days) but slowed down after approximately 30 days. A correlation coefficient of 0.93 was obtained for fraction released *in vitro* and fraction absorbed *in vivo* as shown in Fig. 9.
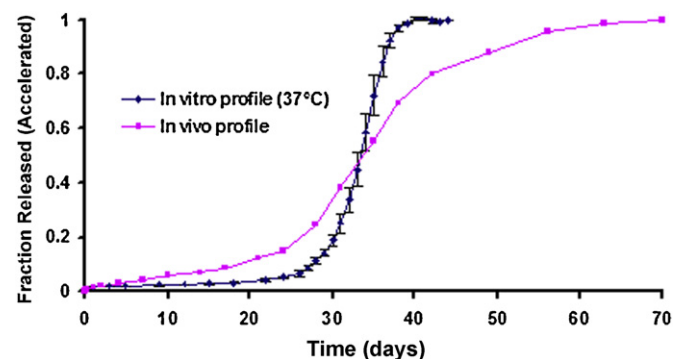

Fig. 8. *In vitro* release (37 °C) and *in vivo* absorption profiles of Risperdal® Consta® 25 mg long acting injection (risperidone microspheres).

Table 1
Pharmacokinetic parameters calculated using GastroPlus™ software (Simulations Plus, Inc., CA) from the reported intravenous risperidone data (1 mg) (Huang et al., 1993).

A (μg/ml)	B (μg/ml)	α (h^{-1})	β (h^{-1})	k_{10} (h^{-1})	k_{12} (h^{-1})	k_{21} (h^{-1})	$t_{1/2}$ (h)
0.016 ± 0.002	0.008 ± 0.003	0.340 ± 0.134	0.037 ± 0.005	0.098 ± 0.031	0.152 ± 0.081	0.126 ± 0.032	19.060 ± 2.784

A and B are empirical constants; α and β are the hybrid rate constants of the distribution and elimination phases, respectively.
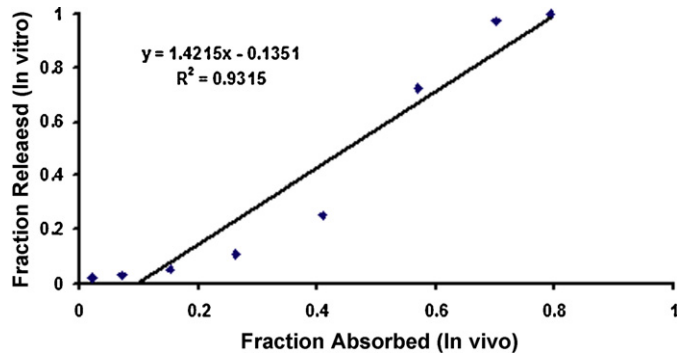

Fig. 9. Plot of fraction released *in vitro* (37 °C) and fraction absorbed *in vivo*.
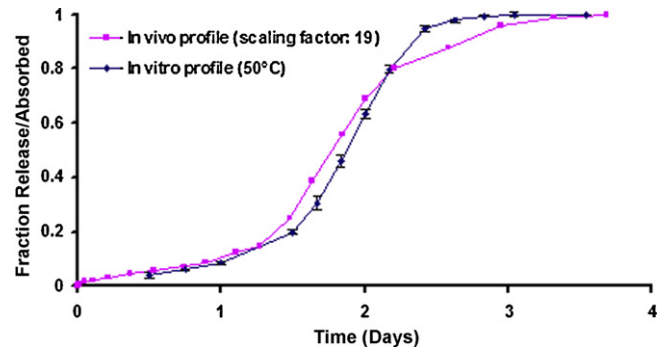

Fig. 12. *In vitro* release (50 °C) and *in vivo* absorption profiles (time scaled) of Risperdal® Consta® 25 mg long acting injection (risperidone microspheres).

Fig. 10. *In vitro* release (45 °C) and *in vivo* absorption profiles (time scaled) of Risperdal® Consta® 25 mg long acting injection (risperidone microspheres).
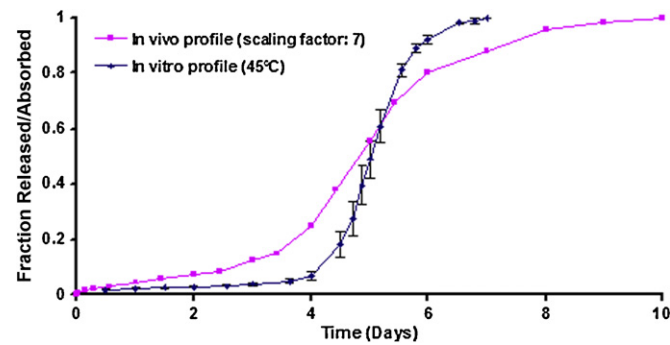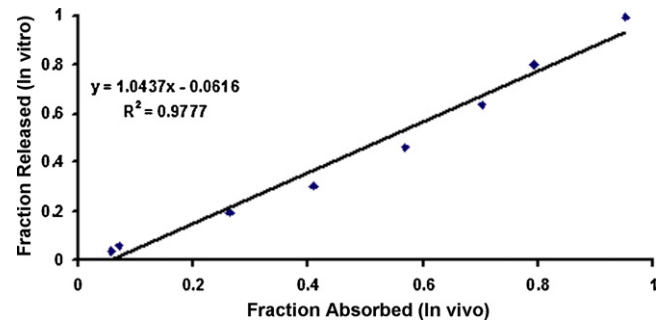

Fig. 13. Plot of fraction released *in vitro* (50 °C) and fraction absorbed *in vivo*.

Accelerated *in vitro* release profiles were also compared with the time scaled *in vivo* profile. Scaling factors were determined as the ratios of time to 50% drug released/absorbed in the *in vivo* and *in vitro* (accelerated) profiles. The trend in the *in vitro* release profiles at 37 and 45 °C was similar (Fig. 1). Similar to the real-time release profile, the accelerated *in vitro* release profile at 45 °C resulted in a correlation coefficient of approximately 0.93 with the *in vivo* profile (Figs. 10 and 11). However, the profiles at 50 and 54.5 °C overlapped with the time scaled *in vivo* profile with correlation coefficients of 0.97 and 0.99, respectively (Figs. 12–15).
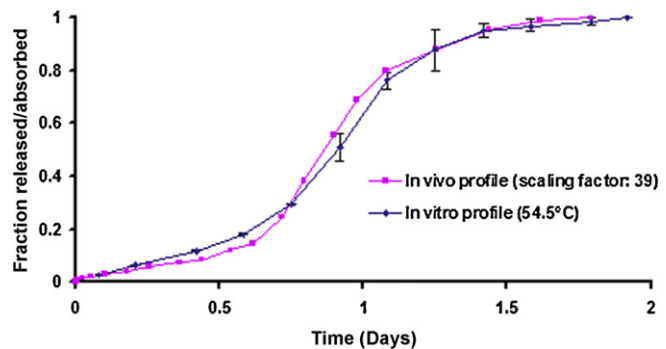

Fig. 14. *In vitro* release (54.5 °C) and *in vivo* absorption profiles (time scaled) of Risperdal® Consta® 25 mg long acting injection (risperidone microspheres).
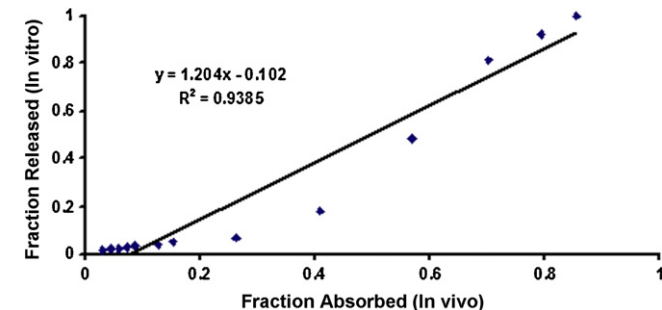

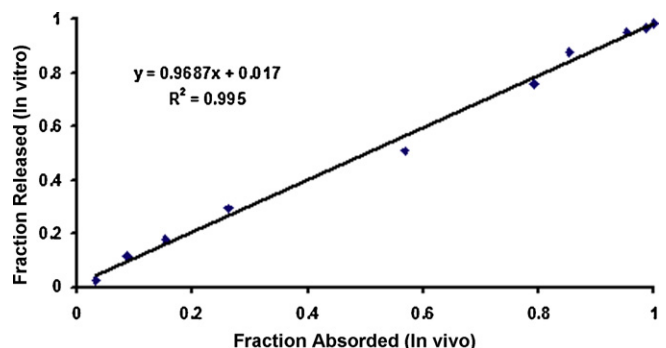**Fig. 11.** Plot of fraction released *in vitro* (45 °C) and fraction absorbed *in vivo*.

Fig. 15. Plot of fraction released *in vitro* (54.5 °C) and fraction absorbed *in vivo*.

4. Discussion

The use of elevated test temperatures is one of the simplest ways of achieving accelerated drug release from the PLGA microspheres. However, drug degradation in the release medium is a concern at elevated temperatures. In the present work, the stability of risperidone in the release media at 37, 45, 50 and 54.5 °C allowed accelerated release testing of Risperdal® Consta® microspheres (risperidone microspheres) at these temperatures.

A significant reduction in the *in vitro* release duration of the Risperdal® Consta® microspheres at elevated temperatures (from approximately 40 days at 37 °C to 7, 3 and 2 days at 45, 50 and 54.5 °C, respectively (Fig. 2)) is considered to be due to an increase in the PLGA degradation rate and drug diffusion through the polymeric matrix. The increase in the first order polymer degradation rate constants with increase in temperature has been reported earlier for PLGA microspheres (Zolnik et al., 2006). The overlapping *in vitro* release profiles of the microspheres at 37 (time scaled) and 45 °C and a correlation coefficient of 0.9929 (Fig. 1) suggests that the drug release mechanism was the same at both temperatures. The drug release mechanism from the PLGA microspheres is a combination of polymer erosion and drug diffusion (Faisant et al., 2002). However, depending upon the PLGA molecular weight and composition, either polymer degradation or drug diffusion can be the predominant rate controlling mechanism (Faisant et al., 2002; Zolnik et al., 2006). Deviation of the release profiles at 50 and 54.5 °C from the time scaled real-time (37 °C) release profile and the decrease in correlation coefficient (R^2) from approximately 0.99 (at 45 °C) to 0.95 (at 50 and 54.5 °C) (Figs. 3–6) can be explained on the basis of the glass transition temperature (Tg $\sim$ 48 °C) of the microspheres. Increase in temperature above the Tg increases the molecular mobility and free volume in the polymeric microspheres and consequently there is an increase in the polymer degradation rate and drug diffusion through the polymeric matrix (Allison, 2008; Faisant et al., 2002; Liu et al., 2006). This may have resulted in a change in drug release mechanism of the microspheres at 50 and 54.5 °C. Significantly faster polymer degradation and drug release rates have been reported for PLA (poly (D-L-lactide)) and PLGA microspheres above their glass transition temperatures (Aso et al., 1994; Shameem et al., 1999).

The disparity between deconvoluted *in vivo* profile and real-time *in vitro* profile (faster *in vivo* release/absorption during the lag phase and slow release/absorption after approximately 30 days (Fig. 8)) can be attributed to the difference in the conditions between the *in vivo* environment and the *in vitro* test. A faster *in vivo* release/absorption during the lag phase (first 24 days) is considered to be due to the accumulation of acidic PLGA degradation products and hence lowering of the pH both inside and in the interstitial space immediately surrounding the microspheres. This may result in rapid auto-catalyzed PLGA degradation and a faster release profile. Faster release *in vivo* compared to *in vitro* has been reported in the literature for PLGA microspheres (Jiang et al., 2002; Zolnik and Burgess, 2008). Tracy et al. (1999) have reported the *in vivo* PLGA degradation rate to be 1.7–2.6 times faster than *in vitro* regardless of polymer molecular weight and end groups. A change in the mechanism of release from bulk erosion to surface erosion under *in vivo* conditions (due to lowering of the local pH) has been reported (Chu et al., 2006; Zolnik and Burgess, 2008). The slower *in vivo* release/absorption after day 30 is speculated to be due to chronic inflammation in response to the presence of microspheres in the interstitial site. This can result in fibrosis and consequent isolation of the microspheres which may slow down drug absorption (Anderson et al., 1993).

Although, the accelerated *in vitro* release profile obtained at 45 °C (below the glass transition temperature of the microspheres) can be useful for quality control testing of the microspheres as it reduces the test duration and showed a good linear correlation ($R^2 \sim 0.99$) with the real-time *in vitro* release profile (Fig. 1), there was lack of *in vivo* relevance at this temperature ($R^2 \sim 0.93$) (Figs. 10 and 11). The increase in the polymer degradation and drug diffusion rates above the glass transition temperature of the microspheres (Tg $\sim$ 48 °C) under *in vitro* conditions was advantageous in terms of establishing a one-to-one linear relationship with the entire time scaled *in vivo* profile ($R^2 \sim 0.97$ at 50 °C and 0.99 at 54.5 °C) (Figs. 12–15). However the profiles did not show a good linear correlation with the real-time *in vitro* release profile (Figs. 3–6).

The accelerated *in vitro* release profiles (50 and 54.5 °C) obtained above the glass transition temperature of the microspheres reduced the test duration from approximately 40 days (at 37 °C) to 3 and 2 days (at 50 and 54.5 °C, respectively) and showed a linear one-to-one relationship with the *in vivo* profile. Accordingly, this method can be used for both: quality control of microsphere products as well as for their *in vivo* performance prediction without the need of simulating the complex *in vivo* conditions.

5. Conclusions

The *in vitro* release profiles of Risperdal® Consta® microspheres obtained at temperatures above the glass transition temperature correlate well with the time-scaled *in vivo* release profile. The polymer degradation profile and rate as well as the drug diffusion increases significantly above the glass transition temperature of PLGA microspheres. It appears that this change resulted in *in vitro* release profiles that were comparable to the time-scaled *in vivo* profile considering faster *in vivo* polymer degradation (compared to the real-time *in vitro* degradation rate). This work shows the importance of the glass transition temperature of the microspheres in selecting appropriate conditions (temperature) for accelerated release testing. Separate *in vitro* release methods are often developed for quality control and *in vivo* performance prediction of complex parenterals since a simple accelerated *in vitro* method is preferred for quality control purposes, whereas more complex conditions are usually required to establish a bio-relevant method. The present work shows that through appropriate selection of conditions, a simple *in vitro* release test can be developed that may be applicable for both quality control purposes and the establishment of an *in vitro*–*in vivo* relationship for other PLGA and polymer based controlled drug delivery systems.

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